Conclusions: Canonical wnt expression and subsequent WISP1 is increased in the synovium during experimental OA. This synovial expression may lead to the degradation of cartilage, possibly by change of the articular chondrocyte phenotype. This change of chondrocyte phenotype may be induced by change of the TGFβ signaling route from the smad2P route to the smad1,5,8 route. Canonical wnt signaling stabilizes smad1,5,8, whereas WISP1 has been shown to inhibit smad2 phosphorylation (Inkson et al. *J Cell. Biochem.* 2008). This indicates synovial wnt expression as a potential target for OA therapy.

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TYPE 3 FINGER LENGTH PATTERN IS ASSOCIATED WITH TOTAL KNEE (TKR) BUT NOT WITH HIP REPLACEMENTS (THR) IN THE ELDERLY: THE AGES-REYKJAVIK STUDY

K. Sigurjonsdottir[1], T.M. Bjorgulfsson[1], T. Aspelund[2,1], G. Eiriksdottir[2], S. Sigurdsson[2], T. Ingvarsson[3], T.B. Harris[4], L. Launer[4], V. Gudnason[2,1], H. Jonsson[5]
[1]Univ. of Iceland, Reykjavik, Iceland; [2]Icelandic Heart Association, Kopavogur, Iceland; [3]Central Hosp., Akureyri, Iceland; [4]Natl. Inst. on Aging, Bethesda, MD; [5]Landspitalinn, Univ. of Iceland, Reykjavik, Iceland

Purpose: Recent case-control studies have shown an association between type 3 finger length pattern (longer ring finger than index finger) and knee osteoarthritis. This study tests the hypothesis that the type 3 pattern is associated with total joint replacements (TJR) due to osteoarthritis in a large population based study.
Methods: In this population-based multidisciplinary study of aging in the elderly population of Reykjavik, Iceland, the prevalence of OA caused TKR was 223 (4.3%) and THR 316 (6.1%). Finger length ratios were assessed visually on 5170 hand photographs (2975 females, 2195 males, mean age 76±6 years). For comparison, similar visual readings were done with 371 hand radiographs (211 females, 160 males mean age 75.6±4.8) from the same group. Exact (pixel) measures of the fingers and metacarpals were also obtained in this sample.
Results: Visual assessments of finger lengths overestimated the pixel 2D:4D ratio which was on average 0.91±0.02 and less than 1 in all cases. According to visual assessments of the radiographs, 64% had type 3 pattern (54% in females, 78% in males). Visual assessment of photographs had an even lower prevalence of the type 3 pattern 50% (43% in females 58% in males). In the photographic assessment there were associations with age (higher prevalence of type 3 pattern) height (lower prevalence) and metacarpal 2:4 ratio (lower prevalence). Correlation between the two methods was 0.65.
We then performed a backwards binary logistic regression analysis for TKR and THR, including finger length patterns, OA at other sites and other variables with possible association to OA such as age, gender, abdominal circumference, BMI, hs-CRP, cholesterol, statin use, bone mineral density of the spine, education and smoking history. The regression analysis revealed an odds ratio for TKR of 1.65 (1.24-2.2) p=0.0007, in the type 3 finger pattern group, similar in both genders. No association was seen between finger length patterns and THR. In the much smaller radiography sample, unadjusted OR for TKR was 1.9 (0.6-5.8) in the type 3 finger group, not significant.
Conclusions: Finger length patterns can be read from digital photographs but the method seems to underestimate the prevalence of type 3 finger length pattern compared with radiographic readings. It may also be confounded by age, height and metacarpal ratio. Nevertheless there is a clearly significant association between the type 3 pattern and TKR but not THR in both genders in this elderly group.

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REQUIREMENT OF SYNOVIAL PERLECAN FOR OSTEOPHYTE FORMATION IN OSTEOARTHRITIS

H. Kaneko[1,2], M. Ishijima[1,2], I. Futami[1,2], N. Ichikawa[3], E. Hirasawa-Arikawa[3], K. Kaneko[1,2]
[1]Dept. of Med. for Motor Organ, Juntendo Univ. Graduate Sch. of Med., Tokyo, Japan; [2]Dept. of orthopedics, Juntendo Univ. Sch. of Med., Tokyo, Japan; [3]Res. Inst. for Disease of Old Age, Juntendo Univ., Graduate Sch. of Med., Tokyo, Japan

Purpose: Osteoarthritis (OA) is primarily characterized by cartilage degradation. However, osteophyte formation, as well as subchondral bone sclerosis, cysts, and synovial inflammation, are also observed in the development of OA. The osteophyte, which is one of the signs of severe OA, is a bony outgrowth at the margins of the joint. Transforming growth factor (TGF)-β is involved in this process. However, its precise molecular mechanisms still remain unclear.
Perlecan is a heparan sulfate proteoglycan present in all basement membranes, cartilage and synovium. Perlecan interacts with extracellular matrix proteins, growth factors, and receptors, and is implicated in cell growth, differentiation, and signaling. Functional null-mutations of perlecan cause lethal chondrodysplasia in both mice and humans (Dyssegmental dysplasia, Silverman-Handmaker type (DDSH)). Although perlecan is required for the development of cartilage, the roles of perlecan in synovial tissues and in the development of OA are unknown. The purpose of this study was to investigate the role of perlecan expressed in synovial tissues in the development of knee OA.
Methods: The perlecan-null (*Perl*$^{-/-}$) mice die perinatally because of premature cartilage development. To restore cartilage abnormalities, we created the lethality-rescued mice (*Perl*$^{-/-}$*;Col2-TgPerl*) by mating heterozygous perlecan-null (*Perl*$^{+/-}$) mice with transgenic (*Col2-TgPerl*) mice, which expressed recombinant perlecan in cartilage using a cartilage-specific *Col2a1* promoter. In intra-articular tissues of *Perl*$^{-/-}$*;Col2-TgPerl* mice, perlecan was expressed in chondrocytes but not in the synovium. Hetrozygous perlecan null mice with the transgene (*Perl*$^{+/-}$*;Col2-TgPerl*) were used as control. Two procedures were used to induce knee OA in 12-week-old female mice. Study1 (instability model): Left knee joints of the mice were subjected to surgical induction of OA by the transduction of medial collateral ligament and resection of medial meniscus, while right knee joints of the mice were subjected to sham-operation by capsulectomy. Study2 (TGF-β model): Left knee joints of the mice were injected i.a. with TGF-β (200 ng) three times on alternate days. The mice were sacrificed at 1, 2, 4 and 8 weeks after either the surgery or the injection. The development of OA in the mice was histologically evaluated.
Results: In *Perl*$^{-/-}$*;Col2-TgPerl* mice, perlecan was expressed in the pericellular matrix of chondrocytes in both articular cartilage and growth plates, but not in the lining or sublining layers of synovial tissues, while control mice expressed perlecan in all these tissues. In the Study1 OA model, the medial side of the left knee joints in both control and *Perl*$^{-/-}$*;Col2-TgPerl* mice resulted in the OA exhibiting cartilage destruction, osteophyte formation, and synovial inflammation 4 weeks after surgery, while the right knees did not show any changes. There were no significant differences in scores of cartilage destruction and synovitis of the joints in *Perl*$^{-/-}$*;Col2-TgPerl* and control mice. However, the osteophyte size and maturation in the joints were significantly reduced in *Perl*$^{-/-}$*;Col2-TgPerl* mice compared with those in control mice ($p<0.05$). In the Study2 OA model, osteophytes were induced by TGF-β in both *Perl*$^{-/-}$*;Col2-TgPerl* and control mice, similar to that observed in the Study1 OA model. However, the size and maturation of osteophytes in *Perl*$^{-/-}$*;Col2-TgPerl* mice were also significantly reduced compared with those in control mice ($p<0.05$).
Conclusion: Our study using two different *in vivo* OA models demonstrates that the osteophyte formation in OA is inhibited due to the absence of perlecan in the synovium. Thus perlecan in the synovium is critical to osteophyte formation, probably through TGF-β signaling.

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R-SPONDINS ARE NEW PLAYERS IN OSTEOARTHRITIS THAT REGULATE WNT SIGNALING IN OSTEOBLASTS

É. Abed, T. Chan, A. Delalandre, D. Lajeunesse
CRCHUM, Hôpital Notre-Dame, Montréal, QC, Canada

Purpose: Clinical and *in vitro* studies suggest that subchondral bone sclerosis and altered bone remodeling, due to abnormal osteoblasts (Ob), is involved in the progression and/or onset of osteoarthritis (OA). Moreover, human OA subchondral Ob show a phenotype of very differentiated cells, however they fail to mineralize normally *in vitro* as *in vivo*. Wnt signaling plays a key role in osteogenesis by promoting the differentiation and mineralization of Ob mainly via the canonical Wnt/β-catenin signaling pathway. R-spondins (Rspo), a new family of 4 proteins structurally unrelated to other Wnt ligands, can act as Wnt agonists and in particular they can oppose the inhibition of Wnt/β-catenin signalling by Dickkopf-1 and -2. Two of the Rspo family members are present in bone tissues, Rspo1 and Rspo2, yet we still have no data on their potential role in OA. Here we investigated the presence of Rspo-1 and -2, their potential upstream effectors, and their role in OA Ob.